UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,410	04/17/2001	Robert L. Gendron		7267

7590 04/11/2003

Frost Brown Todd LLC
2200 PNC Center
201 East Fifth Street
Cincinnati, OH 45202

EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/11/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application N .	Applicant(s)	
	09/836,410	GENDRON ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- Th MAILING DATE f this communicati n appears n the cover sheet with the c rrespondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 28, 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 50-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,4,5,50,51,54 and 74-79* is/are allowed.

6)☒ Claim(s) *53,55-62,64-73 and 80-87* is/are rejected.

7)☒ Claim(s) *52 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

It is noted that Applicant has requested that the requirement for a new oath or declaration in compliance with 37 CFR 1.67(a) be held in abeyance.

Claim Objections

The objections to claims 9, 12, 16, 41 and 44, set forth in the prior Office action, mailed July 26, 2002, are withdrawn in response to Applicant's amendments filed January 28, 2003. New objections, in response to the amendments filed January 28, 2003, are set forth below.

Claim 52 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 52 does not further limit claim 51, because it recites an intended use for the composition of claim 51. An intended use does not change the composition and, therefore, claim 52 is drawn to the same composition as claim 51 and does not further limit claim 51.

Claim 53 is objected to because of the following informalities: Claim 53 contains several typos in line one, such that spaces occur within words and spaces are missing between words. Specifically, the words "T he", "i solated", "a ntisense", "n ucleic", "C laim" and "c onsisting", should be amended to read "The", "isolated", "antisense", "nucleic", "Claim" and "consisting", respectively. A space should be

inserted between the words "of" and "the" at the end of line one. Appropriate correction is required.

Claim 56 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 56 does not further limit claim 55, because it recites a latent characteristic for the composition of claim 55, which is inherent to the composition of claim 55, therefore, claim 56 is drawn to the same composition as claim 55 and does not further limit claim 55.

Claim 61 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 61 does not further limit claim 60, because it recites a latent characteristic for the composition of claim 60, which is inherent to the composition of claim 60, therefore, claim 61 is drawn to the same composition as claim 60 and does not further limit claim 60.

Claim 63 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 63 does not further limit claim 51, because it recites an intended use for the composition of claim 51. An

intended use does not change the composition and, therefore, claim 63 is drawn to the same composition as claim 51 and does not further limit claim 51.

Claim 67 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 67 does not further limit claim 66, because it recites a latent characteristic for the composition of claim 66, which is inherent to the composition of claim 66, therefore, claim 67 is drawn to the same composition as claim 66 and does not further limit claim 66.

Claim 69 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 69 does not further limit claim 66, because it recites a latent characteristic for the composition of claim 66, which is inherent to the composition of claim 66, therefore, claim 69 is drawn to the same composition as claim 66 and does not further limit claim 66.

Claim 72 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 72 does not further limit claim 71, because it recites a latent characteristic for the composition of claim 71,

which is inherent to the composition of claim 71, therefore, claim 72 is drawn to the same composition as claim 71 and does not further limit claim 71.

Claim Rejections - 35 USC § 112

The rejections of record of claims 6-49 under 35 USC 112, second paragraph, set forth in the prior Office action, mailed July 26, 2002, are withdrawn in response to Applicant's amendments filed January 28, 2003.

The rejections of record of claims 2-5, 8, 11-13, 15-17, 19-22, 24-28, 30-35 and 41-49, under 35 U.S.C. 112, first paragraph as lacking adequate written description, set forth in the prior Office action, mailed July 26, 2002, are withdrawn in response to Applicant's amendments filed January 28, 2003.

The rejections of record of claims 15-33 and 46-49, under 35 U.S.C. 112, first paragraph as lacking enablement, set forth in the prior Office action, mailed July 26, 2002, are withdrawn in response to Applicant's amendments filed January 28, 2003.

New rejections under 35 USC, 112, first and second paragraph, are set forth below, in response to the amendments filed January 28, 2003.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53, 55-62, 56, 57, 64-73, 83 and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 53 recites the limitation "The isolated first antisense molecule" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim, because it depends from claim 52, which does not recite an isolated first antisense molecule. Claim 53 depends from claim 52, which is drawn to an isolated nucleic acid molecule. Claim 52 recites a use for this isolated nucleic acid molecule as for use in generating a first antisense molecule. It is unclear if claim 53 is drawn to the isolated nucleic acid molecule, wherein the isolated nucleic acid molecule is used to generate the first antisense molecule specified in claim 53, or whether claim 53 is drawn to the first antisense molecule generated by the isolated nucleic acid molecule. Claims 55-62 are rejected for the same reasons due to dependence on claim 53.

Claim 56 is indefinite due to the recitation "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 57 recites the limitation "said native, genomic DNA molecule or fragment thereof" in lines 2-3 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 57 is further indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic

DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 58 is unclear because it recites an antisense molecule capable of being transcribed into an antisense mRNA, that blocks translation of tbdn-1 mRNA, wherein the antisense molecule consists of SEQ ID NO:3 (as recited in the parent claim 53). SEQ ID NO:3 is antisense to tbdn-1 mRNA and, therefore, would be transcribed into its complement, which would be the sequence of tbdn-1 mRNA (coding strand) and would not be antisense and, therefore, would not inhibit translation. It is unclear if the antisense molecule claimed is SEQ ID NO:3 or the complement of SEQ ID NO:3, which would be capable of being translated into SEQ ID NO:3, the antisense molecule. Claims 59-62 are indefinite for the same reasons due to dependence on claim 58.

Claim 59 is indefinite because it recites an antisense mRNA molecule of at least 15 nucleobases. Claim 59 depends from claim 53, which recites an antisense molecule wherein the molecule consists of SEQ ID NO:3, which is 1413 nucleobases in length. It is unclear what the limitation "at least 15 nucleobases" imparts to the claim, since the limitations of the parent claims require the antisense to consist of SEQ ID NO:3 (1413 bases).

Claims 59 and 60 are indefinite because they recite "The first antisense tbdn-1 mRNA of Claim 58", wherein claim 58 is drawn to an isolated first nucleic acid molecule, which is capable of being transcribed into an antisense tbdn-1 mRNA. It is unclear if claims 59 and 60 are drawn to an isolated first nucleic acid molecule capable of being

transcribed into the tbdn-1 mRNA specified in claim 59 and 60, or whether claim 59 and 60 are drawn to the first antisense tbdn-1 mRNA specified in the claim. Claims 61 and 62 are indefinite for the same reasons due to dependence on claim 60.

Claim 61 is indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 62 is indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 64 recites the limitation "The isolated first antisense molecule" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim, because it depends from claim 63, which does not recite an isolated first antisense molecule. Claim 64 depends from claim 63, which is drawn to an isolated nucleic acid molecule. Claim 64 recites a use for this isolated nucleic acid molecule as for use in generating a first antisense molecule. It is unclear if claim 64 is drawn to the isolated nucleic acid molecule, wherein the isolated nucleic acid molecule is used to generate the first antisense molecule specified in claim 63, or whether claim 64 is drawn to the first antisense molecule generated by the isolated nucleic acid molecule. Claims 65-73 are indefinite for the same reasons due to dependence on claim 64.

Claim 67 is indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 68 is indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 69 is unclear because it recites an antisense molecule capable of being transcribed into an antisense mRNA, that blocks translation of tbdn-1 mRNA, wherein the antisense molecule consists of SEQ ID NO:4 (as recited in the parent claim 64). SEQ ID NO:4 is antisense to tbdn-1 mRNA and, therefore, would be transcribed into its complement, which would be the sequence of tbdn-1 mRNA (coding strand) and would not be antisense and, therefore, would not inhibit translation. It is unclear if the antisense molecule claimed is SEQ ID NO:5 or the complement of SEQ ID NO:4, which would be capable of being translated into SEQ ID NO:4, the antisense molecule. Claims 70-73 are indefinite for the same reasons due to dependence on claim 69.

Claim 70 is indefinite because it recites an antisense mRNA molecule of at least 15 nucleobases. Claim 70 depends from claim 64, which recites an antisense molecule wherein the molecule consists of SEQ ID NO:4, which is 3418 nucleobases in length. It is unclear what the limitation "at least 15 nucleobases" imparts to the claim, since the

limitations of the parent claims require the antisense to consist of SEQ ID NO:4 (3418 bases).

Claim 72 is indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 73 is indefinite because it recites "native, genomic tbdn-1 mRNA". It is unclear how an mRNA can be genomic, as mRNA is transcribed from genomic DNA. The term "genomic mRNA" is not a term of art, nor is it defined in the specification, and therefore, the metes and bounds of the claimed molecules are unclear.

Claim 83 is indefinite because it is unclear how a method comprises a chemotherapeutic agent. This rejection would be obviated if the word "administering" were inserted before the word "chemotherapeutic".

Claim 87 is indefinite because it is unclear how a method comprises a chemotherapeutic agent. This rejection would be obviated if the word "administering" were inserted before the word "chemotherapeutic".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for limiting the growth of tumor cells in

vitro (cell culture) or limiting the growth of tumor cells treated ex vivo with antisense and implanted into an organism, does not reasonably provide enablement for methods of limiting the growth or metastasis of tumor cells in vivo (whole organism) wherein the treatment is in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 80-87 are drawn to methods for limiting the growth or metastasis of tumor cells expressing tbdn-1 by administering a therapeutically effective amount of an antisense molecule targeted to tbdn-1 of SEQ ID NO:3 or 4 to tumor cells, or by administering a composition comprising a vector and an antisense of SEQ ID NO:3 or 4 to tumor cells, and inhibiting the expression of tubedown-1 protein. Further limitations include these methods wherein radiotherapy and chemotherapeutic agents are also administered to the tumor cells. These claims encompass methods wherein tumor cells in vivo (whole organism) are limited in growth or metastasis and wherein a treatment effect is realized, including treatment for osteosarcoma, including Ewing's sarcoma.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 80-87 are drawn to methods of treatment and delivery of antisense that require a vector expressing antisense to be delivered to generally any target tumor cell in an organism. The claimed methods would require that antisense, or a vector expressing antisense, be delivered to a tumor cell at a concentration effective to inhibit the expression of tubedown-1 to a level that would result in inhibition of tumor growth or metastasis, and would encompass methods that result in a treatment effect for osteosarcoma. The claimed methods depend on inhibition of tubedown-1 protein expression to inhibit tumor cell growth and metastasis and to realize a treatment effect for osteosarcoma, as contemplated in the specification.

The specification has provided examples wherein EWS-96 cells are transfected in vitro with a vector expressing antisense targeted to tubedown-1 and the expression of tubedown-1 is inhibited. The specification has provided examples wherein EWS-96 cells are transfected with a vector expressing antisense targeted to tubedown-1 and these cells are transplanted into immune compromised mice. EWS-96 cells transfected with a vector expressing antisense targeted to tubedown-1 grow more slowly in this xenograft mouse model relative to EWS-96 cells that do not express tubedown-1 antisense.

The specification does not provide any examples wherein antisense is delivered to cells in vivo (whole organism), nor wherein a vector expressing an antisense targeted to tubedown-1 is delivered to cells in vivo (whole organism). The specification has not provided any examples wherein a treatment effect for osteosarcoma is provided using antisense targeted to tubedown-1. The specification has not provided any examples

wherein the metastasis of a tumor cell is limited by inhibiting the expression of tbdn-1 using antisense or a vector expressing the antisense. The one example provided using in vivo (whole organism) data does not appear to be relevant to the treatment methods encompassed in the claimed methods, for example, the specification has not provided any guidance on how to treat osteosarcoma by implanting tumor cells expressing tubedown-1 antisense into an organism. The one example provided using in vivo (whole organism) data does not appear to address the scope of the methods claimed, for example, in the mouse model presented, tumor cells were treat ex vivo with antisense, then the tumor cells were transplanted into the mouse. Delivery and sustained expression of an antisense or vector was not required and this ex vivo treatment method does not seem feasible to inhibit the growth or metastasis of a tumor already existing in an organism.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved

in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant inhibition of tumor cell growth or metastasis, as claimed, particularly for a therapeutic outcome. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of tubedown-1 is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p

79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The claimed methods are further drawn to methods that require the delivery and expression of a vector expressing an antisense targeted to tubedown-1. These gene therapy methods have additional hurdles in vivo (whole organism). Gene therapy methods are further complicated by problems with low expression, unpredictable loss of expression and unpredictable, possibly lethal, immune responses (see for example, Verma, Anderson). For example, gene therapy methods require expression of the antisense molecule to be high enough, and sustained long enough, to inhibit tubedown-1 such that it results in a therapeutic effect. Treatment methods for osteosarcoma would particularly require sustained expression. Expression of vectors *in vivo* (whole organism) is unpredictable, often too low for therapeutic effects or unexpectedly turned off (see Verma et al., for example). Effective expression requires an appropriate promoter-enhancer combination, "the search for such combinations is a case of trial and error for a given type of cell"(see Verma, for example, p 240). The one example

provided by the specification wherein a vector expressing tubedown-1 antisense is used to inhibit the expression of tubedown-1 is wherein the vector is introduced into cells in vitro and these cells are transplanted into a mouse. This example would not provide any guidance for delivering a vector to osteosarcoma cells in an organism in vivo (whole organism).

Due to the lack of specific guidance, one skilled in the art would need to practice undue trial and error experimentation to practice the methods of treatment, as claimed, over the full scope claimed. This experimentation would require the determination of how to specifically deliver tubedown-1 antisense, or a vector expressing such, at a concentration effective enough to result in inhibition of the growth or metastasis of tumor cells in vivo(whole organism) or to achieve a treatment effect, or, in the case of vector delivered antisense, in a manner that results in high enough expression, or sustained expression, to result in an inhibition of tumor cell growth or metastasis or result in a treatment effect being obtained. This would require the determination of compositions, dosages, routes of administration, regions of the tubedown-1 gene accessible to antisense *in vivo*, and effective promoter-enhancer combinations for expression of tubedown-1 antisense in a particular target cell. Due to the lack of specific guidance in the instant specification, one skilled in the art would need to determine these factors *de novo* and, due to the lack of predictability exhibited for methods of treatment using antisense or gene therapy methods, one skilled in the art would not even predict that this undue experimentation would result in a method which

can result in inhibition of tumor cell growth or metastasis for tumor cells in vivo(whole organism) or result treatment effects for osteosarcoma.

Therefore, due to the broad breadth of the claims, the nature of the invention, the high unpredictability of the art, the lack of sufficient guidance provided by the inventor, the lack of working examples, and the quantity of experimentation required, it would have required undue trial and error experimentation for one skilled in the art to practice the invention as claimed, over the full scope claimed.

Conclusion

Claims 1, 4, 5, 50, 51 and 54 are allowable as the prior art does not teach or disclose a nucleic acid consisting of SEQ ID NO: 2. Claims 74-79 are allowable because SEQ ID NO:3 and 4 are free of the prior art and the claimed compositions are useful in tumor cells in vitro, for example.

Claims 52 and 63 are objected to.

Any rejection of record not repeated herein is considered to be withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
April 7, 2003

Karen A. Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER